REMARKS

Claims 37-60 are in this application. Claims 37-43 and 59-60 have been examined; claims 44-58 have been withdrawn. Claims 37, 42-45, 47, 49, 53, 56 and 59-60 have been amended to recite a membrane scaffold protein variant, the recitation of which is supported by the as-filed Specification at page 20, lines 17-19, and at page 26, line 12. None of the amendments made herein constitutes the addition of new matter.

Claims 59-60 are drawn to tandem repeat membrane scaffold protein variants. This is supported by Figures 5E and 5G and their descriptions at page 9, line 25 - page 10, line 2, page 19, lines 1-2, Tables 8, 10 and 18, and the corresponding sequences in the Sequence Listing, as well as at page 20 and at page 26.

The MSP2 protein (SEQ ID NO:17) was previously been found allowable. The Patent Office had suggested presenting a claim to a genus of membrane scaffold proteins that could be found allowable. Claim 59 is drawn to a tandem repeat membrane scaffold protein variant, and claim 60 recites the three particular examples of tandem repeat membrane scaffold protein variants from the application (SEQ ID NOs:17, 19 and 45 and the portions of same lacking the N-terminal 12 amino acid histidine tags). In accordance with the discussion with the Patent Office, claims to nanoscale particles comprising a tandem repeat membrane scaffold protein variant and a tethered membrane protein have been presented, as well as claims to a method of making such a nanoscale particle. Favorable consideration of these claims is again respectfully requested. In addition, the Patent Office discussed claims to nanoscale particles comprising any membrane scaffold protein together with an integral membrane protein or an embedded membrane scaffold protein and such claims have been presented along with corresponding method of making claims.

The Rejections under 35 U.S.C. 112, second paragraph

Claims 59-60 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection.

The Patent Office has alleged that the Specification has not defined the term "tandem repeat membrane protein" unambiguously and that it is unclear whether the term refers to repeat of an amino acid sequence, a specific structure (such as a helix) or both.

Applicants respectfully point to the as-filed Specification at page 9, line 25 through page 10, line 2. Figs. 5E and 5G illustrate tandem repeat membrane scaffold protein variants. See also page 19, lines 1-10, for a discussion of MSP, a tandem repeat of MSP1, in which the MSP1 (protein) sequences are separated by a short (4 amino acid) linker sequence. See also Tables 8, 10 and 18. The context is clear -- a tandem repeat membrane scaffold protein variant is one in which a large (protein) sequence is repeated, with the protein sequences being separated by an intervening linker (peptide) sequence. It is clearly not a repeat of only a single helical structure or relatively short amino acid sequence.

Applicants respectfully maintain that the context of the application makes the claimed term abundantly clear to one of ordinary skill in the art, and the withdrawal of the rejection is respectfully requested.

The Rejections under 35 U.S.C. 102(b)

Claims 37 and 59 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bayburt et al. (1998). Applicants respectfully traverse this rejection.

Applicants respectfully note that the Bayburt paper describes particles prepared using naturally occurring human apolipoprotein A1; see also Jonas et al. (1989) J. Biol. Chem. 264:4818-4824, where it is made clear that the Bayburt paper relates to

apolipoprotein prepared from human plasma. By contrast, the present application relates to membrane scaffold protein **variants**, as described at pages 20 and 26. The variants are improved in their properties over the naturally occurring human apolipoprotein A1, which was taught in the cited Bayburt 1998 reference. The membrane scaffold variants of the present invention are clearly distinguished from the naturally occurring human protein (isolated from plasma). The amendment of the claims to recite "variant" was for improved clarity; it is not and was never Applicants' intent to read on the use of naturally occurring human apolipoprotein A1 or a recombinant protein identical to human apolipoprotein as it occurs in nature, in conjunction with a tethered membrane protein.

With regard to Applicants' assertion that the amended claims which recite an "artificial" membrane scaffold proteins are distinct in their amino acid sequences from an apo AI protein as disclosed in Bayburt *et al.* has not been deemed to be persuasive because a membrane scaffold protein, *e.g.,* apo AI protein, can be made by DNA recombinant technology and such an artificial scaffold protein can have the same sequence as that of a membrane scaffold protein isolated from a natural source. The Examiner also asserts that the specification fails to unambiguously define an artificial scaffold membrane protein as one that has a distinct amino acid sequence from a naturally occurring scaffold membrane protein. The Examiner concludes that the word "artificial" does not limit the scope of the claimed invention and that the Bayburt *et al.* reference still reads on the limitations of claims 37 and 59. Applicants have amended the claims to recite artificial membrane scaffold protein variants, which is supported at page 20, lines 17-19, and at page 26, line 12, of the as-filed Specification.

Applicants respectfully request reconsideration because the protein and particles described by Bayburt *et al.* differ from those presently claimed. However, it is clear from the context of the specification as filed, that the word "artificial" means, *inter alia*, that the membrane scaffold protein variants of the present invention have amino acid sequences that are different from the naturally occurring amino acid sequences.

"Artificial" is not intended to be, in effect, a process limitation. That is, it is not intended to refer to how the protein is made, *i.e.,* by recombinant technology. The Specification gives numerous non-limiting examples of the kinds of differences in structure between natural apoAI and the artificial membrane scaffold protein variants of the present invention. For example, the Specification describes (artificial) membrane scaffold protein sequences in which certain helices of native apoAI are repeated, deleted or replaced with other helices, or have truncations, or have altered hinge regions. See also pages 14, 19 and 28-29 of the as-filed specification. Because Bayburt *et al.* does not teach such modifications of apo A1, it cannot properly be found to anticipate claims 37 and 59, and therefore the rejection should be withdrawn. The Bayburt papers utilized apolipoprotein as a membrane scaffold protein and that apolipoprotein A1 was isolated from human plasma, a natural source -- therefore the apolipoprotein **must** have been a natural protein. Where the membrane protein incorporated into a nanoscale particle, the membrane scaffold protein is a **tandem repeat** membrane scaffold protein variant.

However, in the interest of advancing prosecution and without acquiescing to the rejection, new claims 37-46 are drawn to nanoscale particles comprising a membrane scaffold protein variant and at least one integral or embedded membrane protein. The Bayburt reference relates to cytochrome P450 reductase, a tethered membrane protein. as defined in the present Specification. Those claims (47-48) drawn to nanoscale particles (and methods) comprising a tethered membrane protein are limited to the use of the membrane scaffold protein (MSP2)as set forth in SEQ ID NO:17, which was said to be allowable, as well as other tandem repeat membrane scaffold proteins. The cited Bayburt reference relates to an apolipoprotein AI protein which is not a tandem repeat membrane protein. Compare, e.g., Tables 2 and 8 of the as-filed application. As discussed in the personal interview, there was no teaching or suggestion in the cited Bayburt reference that an embedded or integral membrane protein could be incorporated into a nanoscale particle, where the protein is maintained in an active conformation, like that of the native protein in a natural membrane environment.

With respect to the allegation that incorporation of an integral protein was taught by the cited Bayburt reference, Applicants respectfully refer to the definitions of types of membrane proteins in the present application, in the paragraph bridging pages 14 and 15.

> Tethered membrane proteins are composed mostly of a relatively soluble globular domain external to the bilayer and relatively simple (e.g., a single pass helix) which anchors this domain to the membrane bilayer. The globular domain, in nature, can be extracellular or cytoplasmic in orientation. Embedded membrane proteins, as defined herein, are those which include a membrane anchoring segment of the polypeptide, but which also have groupings of hydrophobic amino acids on the surface of the protein, which hydrophobic domains are embedded within the membrane bilayer. Integral membrane proteins are predominantly located within the membrane bilayer; relatively small portions of the protein are exposed to an aqueous environment within the cell or to the extracellular aqueous environment.

As supported by the as-filed application, the particles claimed are distinct from those described in the cited Bayburt et al. reference. With respect to the statement of the Patent Office that Applicants cannot distinguish over the cited reference, it is respectfully submitted that Applicants have, in fact, distinguished in two ways -- the recitation of variants of a membrane scaffold protein and in the recitation of integral membrane proteins, as defined in the present application. Applicants submit that they are entitled to be their own lexicographers and that the definitions provided in the present application are in, fact, refined over the usage of the prior art.

Accordingly, it is maintained that the present invention as claimed is not anticipated by the cited prior art and that the amendment to recite variants is not a narrowing amendment. The usage of "artificial" with respect to the naturally occurring lipoprotein actually relates directly to the usage in the Specification of "variant". In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 102(b).

Claim Objections

Claims 42 and 60 were objected to because they recite nonelected subject matter, i.e., the amino acid sequences set forth in SEQ ID NOS: 6, 9, 19, 23, 29 and 43-45.

With respect to claims related to nanoscale particles and methods related to tethered membrane proteins, claims limited to the use of a tandem repeat membrane scaffold protein variant having the amino acid sequence set forth in SEQ ID NO:17 were identified as allowable. In anticipation of allowability of claims to tandem repeat membrane scaffold proteins and their uses in methods and particles, these claims recite tandem repeat membrane scaffold protein variants of SEQ ID NO:17, amino acids 13 to amino acids 13 to 414 of SEQ ID NO:17, SEQ ID NO:19, amino acids 13 to 422 of SEQ ID NO:19, SEQ ID NO:45 and amino acids 13 to 392 of SEQ ID NO:45. Applicants respectfully request that examination be extended to additional exemplary artificial tandem repeat variant sequences. Applicants respectfully request that examination be extended to additional tandem repeat MSP variant sequences.

Claims 38-43 were objected to as being dependent on a rejected base claim. Claim 37 is drawn to a nanoscale particle comprising a membrane scaffold protein variant and an integral membrane protein. Dependent claims 38-43 are drawn to particular types and examples of integral membrane proteins and with respect to the membrane scaffold protein, various engineered membrane scaffold variants. Applicants have also provided a set of method claims identical in scope to those in the claims to particles comprising a membrane scaffold protein variant and an integral membrane protein. Similarly, in accordance with the discussion with the Examiner in the personal interview, Applicants have presented claims drawn to nanoscale particles and methods of incorporating an embedded membrane protein in a nanoscale particle.

Claims 47-48 and 56-58 are drawn to a nanoscale particle comprising a tethered membrane protein and a tandem repeat membrane scaffold variant having the amino

acid sequences set forth in SEQ ID NO:17 (MSP2), amino acids 13 to 414 of SEQ ID NO:17, SEQ ID NO:19, amino acids 13 to 422 of SEQ ID NO:19, SEQ ID NO:45 or amino acids 13 to 392 of SEQ ID NO:45, and methods with the same scope of membrane scaffold protein variant. The sequences of other specifically exemplified tandem repeat membrane scaffold proteins are also recited in claim 60; claim 59 recites the use of a tandem repeat membrane scaffold protein variant. Accordingly, Applicants submit that claims are in condition for allowance. Applicants recognize that there has been a restriction requirement with respect to membrane scaffold proteins and particles; however, rejoinder of method claims with allowable composition claims of the same scope is respectfully requested.

Claim 60 is drawn to a membrane scaffold protein having the amino acid set forth in SEQ ID NO:17, which has been deemed allowable, as well as other exemplary tandem repeat membrane scaffold protein variants with or without a His tag at the N-terminus. Claim 59 is drawn to the genus of tandem repeat membrane scaffold protein variants. Support is found in Tables 8, 10 and 18 as well as at Figures 5E and 5G and descriptions thereof.

Request to Rejoin Nonelected Species

In the Restriction Requirement mailed on March 24, 2003, Applicants were required to elect a species for prosecution in connection with claims 11-13 because the claims are allegedly directed to three species of membrane protein: a tethered membrane protein, an embedded membrane protein, and an integral membrane protein (all in association with a membrane scaffold protein in a nanoscale particle), which were deemed by the Examiner to be patentably distinct. Restriction to a single species was required for further prosecution if no generic claim was held to be allowable. In response, Applicants elected "integral membrane proteins."

As discussed above, Applicants have presented claims 37-43, which are drawn to nanoscale particles comprising integral membrane proteins in conjunction with

membrane scaffold protein variants. Claims 44-46 are drawn to nanoscale particles comprising embedded membrane proteins in conjunction with membrane scaffold proteins variants, and claims 47-48 are drawn to nanoscale particles comprising tethered membrane proteins in conjunction with membrane scaffold protein variants. Applicants submit that in view of the amendments to the claims and for the reasons discussed above, taking the advice of the Examiner and his supervisor into account, the claims now presented are believed allowable. Applicants request withdrawal of the requirement for election of a single species of membrane protein and request rejoinder and reconsideration of claims directed to embedded membrane proteins, as well as tethered membrane proteins in conjunction with tandem repeat membrane scaffold proteins. Applicants have several embodiments of various membrane proteins incorporated into nanoscale particles, and they are entitled to claims of breadth commensurate with their contribution to the art.

Conclusion

Applicants respectfully submit that the pending claims are in condition for allowance and early notification thereof is requested.

If in the interest of expediting prosecution, the Examiner has questions or comments, he is invited to telephone the undersigned at the indicated telephone number.

It is believed that the present Amendment does not necessitate the payment of any fees under 37 C.F.R. 1.16-1.17. If this is incorrect, however, please charge any fees due pursuant to the foregoing Rules to Deposit Account No. 07-1969.

Respectfully submitted,

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